FORM PTO-1390 (Modified) (REV 10-95) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER: SCH 1653

U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR): 09/446328

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/EP98/03658	18 June 1998	20 June 1997

TITLE OF INVENTION
USE OF INTRAVENOUS CONTRAST MEDIA FOR PROJECTION MAMMOGRAPHY

APPLICANT(S) FOR DO/EO/US
Ulrich SPECK et al.

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☐ This is an express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date
5. ☒ A copy of the International Application as filed (35 U.S.C. 371 (c) (2))
   a. ☐ is transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☒ has been transmitted by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☒ A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. ☒ A copy of the International Search Report (PCT/ISA/210).
8. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3))
   a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ have been transmitted by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☒ have not been made and will not be made.
9. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
10. ☐ An oath or declaration of the inventor(s) (35 U.S.C. 371 (c)(4)).
11. ☐ A copy of the International Preliminary Examination Report (PCT/IPEA/409).
12. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371 (c)(5)).

Items 13 to 18 below concern document(s) or information included:

13. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
14. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
15. ☐ A **FIRST** preliminary amendment.
    A **SECOND** or **SUBSEQUENT** preliminary amendment.
16. ☐ A substitute specification.
17. ☐ A change of power of attorney and/or address letter.
18. ☐ Certificate of Mailing by Express Mail
19. ☒ Other items or information:

Letter
Drawings 1 sheet
PCT/IB/304

U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR 1.5)	INTERNATIONAL APPLICATION NO.	ATTORNEY'S DOCKET NUMBER
09/446328	PCT/EP98/03658	SCH 1653

20. The following fees are submitted:.

BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)) :		CALCULATIONS PTO USE ONLY
☒ Search Report has been prepared by the EPO or JPO	$840.00	
☐ International preliminary examination fee paid to USPTO (37 CFR 1.482)	$670.00	
☐ No international preliminary examination fee paid to USPTO (37 CFR 1.482) but international search fee paid to USPTO (37 CFR 1.445(a)(2))	$760.00	
☐ Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2) paid to USPTO	$970.00	
☐ International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(2)-(4)	$96.00	

ENTER APPROPRIATE BASIC FEE AMOUNT =				**$840.00**	
Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☒ 30 months from the earliest claimed priority date (37 CFR 1.492 (e)).				**$130.00**	
CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total claims	17 - 20 =	0	x $18.00	**$0.00**	
Independent claims	1 - 3 =	0	x $78.00	**$0.00**	
Multiple Dependent Claims **(check if applicable)**.			☐	**$0.00**	
TOTAL OF ABOVE CALCULATIONS =				**$970.00**	
Reduction of 1/2 for filing by small entity, if applicable. Verified Small Entity Statement must also be filed (Note 37 CFR 1.9, 1.27, 1.28) **(check if applicable).**			☐	**$0.00**	
SUBTOTAL =				**$970.00**	
Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (f)).			+	**$0.00**	
TOTAL NATIONAL FEE =				**$970.00**	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31) **(check if applicable).**			☐	**$0.00**	
TOTAL FEES ENCLOSED =				**$970.00**	
				Amount to be: refunded	$
				charged	$

☒ A check in the amount of **$970.00** to cover the above fees is enclosed.

☐ Please charge my Deposit Account No. in the amount of to cover the above fees.
A duplicate copy of this sheet is enclosed.

☒ The Commissioner is hereby authorized to charge any fees which may be required, or credit any overpayment to Deposit Account No. **13-3402** A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

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19,544
REGISTRATION NUMBER

20 December 1999
DATE

Filed: 12/20/99
AJZ:jvbp

USE OF INTRAVENOUS CONTRAST MEDIA FOR PROJECTION MAMMOGRAPHY

The invention relates to the use of intravenous contrast media for projection mammography as well as new devices for projection mammography.

Prior Art

For a decade, mammography has been an established and steadily improved x-ray technique for early detection, radiologic identification, characterization, and localization of mammary tumors. In many respects, it is unparalleled in its performance and availability to patients. The greatest drawback is its imperfect detection sensitivity for tumors that are small and without detectable microlime.

Early on, attempts were made to use contrast media to improve projection mammography. For this purpose, suitable preparations were introduced into the milk ducts, and their dispersion into the breast was used for detecting and characterizing lesions. The work of R. Bjørn-Hansen provides a survey: Contrast-Mammography, Brit. J. Radiol. 38, 947-951, 1965. The technique is also known as galactography. The contrast is achieved by concentrated iodine-containing contrast media (> 100 mg of iodine/ml). In addition, contrast media were injected directly into suspicious or tumorous lesions of the

breast either to characterize the latter (e.g., Lehto, M. and Mathiesen, T. I.: Adenography: An Ancillary Diagnostic Method of Circumscribed Lesions of the Breast with a Positive Contrast Agent, Breast Dis, 6, 259-268, 1993) or to label the latter (e.g., Raininko, R.; Linna, M. I.; Rasanen, O: Preoperative Localization of Nonpalpable Breast Tumors. Acta. Chir. Scand, 142, 575-578, 1976). In both cases, undiluted, commercially available contrast media are used directly for visualization.

The intravenous administration of x-ray contrast media for visualization of parenchymatous processes in projection radiography is the very rare exception. It is successful only if the contrast medium actively accumulates in a tissue or organ. In this respect, there are to date two examples: The visualization of the healthy renal parenchyma by the now commonly used urographic agents and the visualization of the healthy liver and spleen parenchyma by emulsions or suspensions of x-ray-opaque substances. Both methods are no longer used (liver, spleen) or are used only in exceptional cases (kidney). It has never been possible to use intravenously administered x-ray contrast media for direct contrasting of tumors of relevant size in projection radiography.

Computer tomography and especially magnetic resonance tomography are known for their very much higher measuring sensitivity for contrast media. It was still a surprise, however, that both techniques made it possible to detect mammary tumors with great reliability after intravenous contrast medium injection (Gisvold, J. J.; Karsell, P. R.; Reese, E.C.: Clinical

Evaluation of Computerized Tomographic Mammography. Mayo Clin Proc 52, 181-185, 1977; Teifke, A.; Schweden, F.; Cagil, H.; Kanczor, H. U; Mohr, W.; Thelen, M.: Spiral-Computertomographie der Mamma [Spiral Computer Tomography of the Breast]. Fortschr. Röntgenstr 161, 495-500, 1994; Heywang, S. H.; Hahn, D.; Schmidt, H.; Krischke, I.; Eiermann, W.; Bassermann, R.; Lissner, J.: MR Imaging of the Breast Using Gadolinium DTPA. J. Comp Ass Tomogr 10, 199-204, 1986.

Even after publication of the contrast enhancement of mammary tumors by intravenous contrast medium administration in CT, the detection sensitivity of projection mammography for iodine-containing contrast media was previously regarded as too low to be able to use this CT-detectable effect in mammography. The usability of the bromine-containing contrast media that are known as less x-ray-opaque or the metal chelate solutions that are available only in lower concentrations for this application is thus even more unlikely. Fritz, S. L.; Chang, C. H. J.; and Livingston, W. H.: (Scatter/Primary Ratios for X-Ray Spectra Modified to Enhance Iodine Contrast in Screen-film Mammography, Med Phys 10, 866-870, 1983) therefore investigate the question of whether a radiation quality that is more suitable for the absorption spectrum of the iodine can be produced by various physical measures. The results of this work still cannot be considered satisfactory, but it is believed that there is some chance for further optimization of the x-ray spectrum.

In the mid-1980's, an attempt was made to use digital subtraction angiography (DSA) with intravenous injection of

contrast media. The process was not accepted since its reliability and sensitivity were too low, and in any case further testing is required (Dean, P.B.; Sickles, E.A.: Invest Radiol 20, 698-699, 1985).

The above-mentioned methods have advantages over conventional projection mammography, but also significant drawbacks such as high cost and limited availability, inadequate detection of the microlime that is important for tumor diagnosis, low spatial resolution, extended testing times, poor accessibility for biopsies, or higher radiation exposure. Although not every drawback applies to every technique, MR and, even more, CT are now used only in a very small proportion of the patients in question, and DSA is virtually not used at all for detecting mammary tumors.

Because of its almost universal availability, low cost and in many respects high performance, an improvement in the projection mammography that is introduced is therefore of great importance with respect to more reliable detection of tumors. In this respect, many tests have already been done. In particular, the recording technique and the film material that is used have been optimized over the decades; and xeroradiography has been tried and tested. New receiver systems and digitization promise further progress. Nevertheless, projection mammography, as far as can be seen now, clearly lies under the sensitivity of the best method to date, contrast-enhanced magnetic resonance tomography.

Description of the Invention

It has now been found, completely surprisingly enough, that projection radiography, which is known as quite contrast medium-insensitive, can, in special cases, improve projection mammography by intravenous contrast medium administration, although the contrast media are very strongly diluted on the way through heart and lung and are not known to actively concentrate in mammary tumors.

The invention therefore relates to the use of intravenous contrast media for the production of a diagnostic agent for projection mammography.

Through the additional intravenous administration of contrast media, projection mammography achieves a sensitivity that is comparable to that of the most modern processes such as magnetic resonance tomography (MRT) while being considerably more versatile and avoiding the costs of MRT. The new process can be implemented simply and without special stress on the patients and provides a significant improvement in

a) sensitivity to the detection of focal lesions in the breast, and

b) additional information on the nature of lesions detected previously.

Its use according to the invention can be done with now available devices and agents, e.g., as follows, if the devices are operated with low radiation energy -- as is common in projection mammography.

The measuring process is preferably performed as follows:

1) A normal mammogram is recorded (pre-contrast image).

2) The patient receives a commonly used urographic x-ray contrast medium at a dose of about 0.5 g to 1.5 g of iodine/kg of body weight that is quickly injected intravenously or infused.

3) 30 seconds to 1 minute after the end of the injection, a second mammogram is recorded (post-contrast image). Other images are optionally recorded up to about 5 minutes after the end of the injection, which, if necessary, can provide additional information on the properties of the lesion.

Devices and device settings of less than 50 kV are suitable for use according to the invention; the use of radiation that corresponds to 20 kV to 40 kV is preferred; a radiation energy of 25 kV to 35 kV is especially preferred.

For use according to the invention, all compounds are suitable that are commonly used for the production of water-soluble urographic contrast media. As examples, there can be mentioned: meglumine or lysine diatrizoate, iothalamate, ioxithalamate, iopromide, iohexol, iomeprol, iopamidol, ioversol, iobitridol, iopentol, iotrolan, iodixanol, and ioxilan (INN).

Iodine-free compounds can also be used, however, such as, e.g.:

1. Contrast media that contain bromine as an imaging element,

2. Contrast media that contain elements of atomic numbers 34, 42, 44-52, 54-60, 62-79, 82, or 83 as imaging elements,
3. Contrast media that contain chelate compounds of elements of atomic numbers 56-60, 62-79, 82, or 83 as imaging elements.

The invention therefore also relates to the use of such iodine-free compounds.

The now commonly used urographic x-ray contrast media are extremely well suited for the above-described process. It was found, surprisingly enough, that unlike in almost every other x-ray process in projection mammography, the element iodine can be exchanged completely or partially for the element bromine. This has also been discussed specifically in the past but has not proven its value in any x-ray process because of the significantly lower radiation absorption of bromine compared to iodine. In this respect, projection mammography represents an exception. It is a novel, surprising use for the compounds that are described in, e.g., EP 0 118 348 A1.

In addition, contrast media that can be excreted and are tolerable and are based on other opacifying elements, molecular and supramolecular structures are also suitable for use according to the invention.

As opacifying elements, mainly those with atomic numbers 34, 42, 44-60, 62-79, 82, or 83 are suitable. The opacifying elements can be bonded covalently to organic molecules or can be present as complexes or integrated into macromolecular

structures. Substances with molecular weights of 10,000 to 80,000 D are especially advantageous. In addition, the individual contrast medium molecule components can be of larger structures, such as associates, liposomes, emulsion droplets and microparticles or nanoparticles (Parvez, Z.; Moncada, R.; Sovak, M., edts.: Contrast Media: Biological Effects and Clinical Application. Vol. III, CRC Press, Boca Raton, Florida 1987, 73-130).

The medium is prepared in a pharmaceutically usual form in physiologically compatible vehicle media, preferably water, while using commonly used adjuvants such as stabilizers (e.g., complexes, complexing agents, antioxidants), buffers (e.g., tris, citrate, bicarbonate), emulsifiers and substances for adaptation to osmolality and electrolyte content as required.

Preferred are contrast media with concentrations of 100 mg of iodine/ml to 500 mg of iodine/ml; especially preferred are nonionic x-ray contrast media with 200 mg of iodine/ml to 400 mg of iodine/ml or a corresponding x-ray opacity when another radiation-absorbing element is selected. The agent can be administered at a dose of 150 to 1500 mg of iodine/kg of body weight (KG).

When bromine-containing compounds are used according to the invention, a concentration of 100 to 500 mg of bromine/ml in the contrast medium is preferred. The dose that can be administered is 100 to 1500 mg of bromine/kg of body weight.

When compounds of the elements of atomic numbers 34, 42, 44-52, 54-60, 62-79, 82, or 83 are used according to the invention,

a concentration of 10 mmol to 2 mol/l -- relative to the imaging element -- in the contrast medium is preferred. The dose that can be administered is 0.1 to 2 mmol/kg of body weight (relative to the imaging element). The range of 0.2 to 0.6 mmol/kg of body weight is preferred.

When the chelate compounds of the elements of atomic numbers 56-60, 62-79, 82, or 83 are used according to the invention, a concentration of 10 mmol to 2 mol/l -- relative to the imaging element -- in the contrast medium is preferred. The dose that can be administered is 0.1 to 2 mmol/kg of body weight (relative to the imaging element). The range of 0.2 to 0.6 mmol/kg of body weight is preferred.

A very advantageous variant of intravenous contrast-projection mammography in the use according to the invention relates to the use of the subtraction technique, which to date has not been introduced in projection mammography. Corresponding processes have proven their value very well in angiography, however. In angiography, again significantly higher local iodine concentrations (in the blood) are also necessary, however, such as can be achieved in mammary tumors. In this respect, the possible use of this technique for detecting smaller lesions was not predictable. The process thus is based on the use of digital image receivers in mammography, which must have site resolution that is sufficient for this testing method. To achieve this resolution in the digital image that is necessary for mammography, it is therefore possible either to work with digital image receivers of small pixel sizes or to use digital image

receivers in connection with the direct-radiographic magnification technique. Both the contrast resolution and site resolution are considerably improved by the combined use of the magnification technique with digital image receivers. As a result, it is specifically the detection of small lesions that is considerably facilitated. The process is essentially based on the following steps:

1) A normal mammogram (pre-contrast image) is recorded. The data are stored.

2) The patient receives a suitable contrast medium at a sufficient dose -- quickly intravenously injected.

3) Starting at 30 seconds after the end of the injection, one or more additional mammograms are recorded and stored.

4) The data that are taken under (1) are correlated (preferably subtracted) with the data that are taken under (3), and the result is correspondingly enhanced and put out as a picture.

5) Optionally, data for speed and for the extent of the increase in contrast medium and for the kinetics of the washing process are calculated and separately visualized.

The invention therefore also relates to a device for projection mammography that is characterized by site resolution that is sufficient for the mammographic testing. This sufficient site resolution is achieved either directly via the resolution capacity of the digital image receiver or is achieved by a

linkage of the digital image receiver and the direct-radiographic magnification technique. The device also contains at least one storage device for the pre-contrast image, at least one storage device for the post-contrast image, at least one computing unit for correlation (especially subtraction) of the various images, and an output device for the calculated mammogram.

Except for the correlation of the time-sequenced images or data records, it is also advantageous to correlate images that were produced with varying radiation energy. Thus, e.g., in the use of bromine-containing compounds according to the invention, an image with a radiation energy of ξ_1 = 35 kV and an image with a radiation energy of ξ_2 = 25 kV can be made, and the stored images can be correlated with one another -- especially subtracted from one another. In this case, suppression of the normal tissue structures in favor of the opacifying, intravenously fed element is also achieved, since the radiation absorption of the tissue in the selected energies differs from that of the contrast medium. By repeated measurement, the time behavior of the contrast medium concentration can also be detected and evaluated using such a device.

Another subject of the invention is therefore a device for projection mammography that is characterized by at least one storage device for an image at a radiation energy ξ_1, at least one storage device for an image at a radiation energy ξ_2, at least one computing unit for correlation of the various images, and an output device for the calculated mammogram.

In standard projection mammography, in each case only one breast is tested. To limit the necessary quantity of contrast medium, it is advantageous in the use according to the invention to test both breasts simultaneously. Devices that allow such testing are not yet known. The subjects of the invention are therefore also devices that are characterized in that they make possible simultaneous testing of both breasts.

Embodiments:

The following examples are to explain the subject of the invention without intending that it be limited to these examples.

Example 1: Phantom Studies

Bismuth-, iodine- and bromine-containing contrast medium solutions ((4S)-4-(ethoxybenzyl)3,6,9-tris(carboxylatomethyl)-3,6,9-triazaundecanoic acid, bismuth complex, disodium salt, iotrolan (INN) or N-cetyl-N,N,N-trimethylammonium bromide) are produced at a concentration of 9.8 mg of Bi/ml, 6 mg of iodine/ml, or 3.8 mg of Br/ml in 2% agar. The agar gels are cut into layers that are 3 mm, 5 mm, or 10 mm thick. The contrast medium-containing gels as well as a control gel with 2.8 mg of NaCl/ml are integrated into an agar block with a thickness of 5 cm. The entire phantom is x-rayed at 28 kV and 63 mA corresponding to a mammogram, whereby the x-ray radiation in each case has to pass through about 4 cm to 5 cm of contrast medium-free agar and 3 mm to 10 mm of contrast medium-containing agar.

Result: Even the contrast medium-containing agar pieces that are only about 3 mm thick are readily detectable. At an equimolar concentration, bromine is, surprisingly enough, about twice as effective as iodine; bismuth is more than three times as effective as iodine (Figure 1).

Figure 1 shows an x-ray image at 28 kV, 63 mA of an agar phantom with embedded contrast medium-containing agar blocks of: a left series with a thickness of 5 mm, a center series with a 10

mm thickness, and a right series with a 3 mm thickness. The blocks of the upper series contain 3.8 mg of bromine/ml, those of the center series contain 6 mg of iodine/ml, and those of the lower series contain 9.8 mg of Bi/ml.

The block with NaCl is not visible.

Example 2: Intravenous Contrast Medium Mammography

In a patient, a 1.5 cm x 0.8 cm breast carcinoma was detected by mammography based on structures, microlime, and biopsy. Pre-operatively a check is to be made for multiple foci; in this respect, a first indwelling cannula is placed in the left arm vein (V. cubitalis) of the patient. Projection mammography is repeated before the contrast medium is administered. Immediately after the original image, the infusion of 3 ml/kg of Ultravist$^{(R)}$-300 (Schering AG, Berlin; active ingredient: iopromide (INN)) begins at a rate of 3 ml/sec. using an automatic injector. The first image after the administration of contrast medium is made 1 minute after the end of the infusion. The positions of the patient and the imaging device remain completely unchanged during this time, just like the imaging conditions with 28 kV of tube voltage and 63 mA.

The images after the injection of the contrast medium show a significantly enlarged area of the contrast medium image relative to the tissue that is defined as the tumor area before the administration of contrast medium, but no additional separate foci that accumulate in the breast.

Claims

1. Use of intravenous contrast media for the production of a diagnostic agent for projection mammography.

2. Use of an agent according to claim 1, characterized in that the intravenous contrast medium contains iodine as an opacifying element.

3. Use of an agent according to claim 1, wherein the intravenous contrast medium contains bromine as an opacifying element.

4. Use of an agent according to claim 1, wherein the intravenous contrast medium contains a compound of the elements of atomic numbers 34, 42, 44-52, 54-60, 62-79, 82, or 83.

5. Use of an agent according to claim 1, wherein the intravenous contrast medium contains a metal chelate of the elements of atomic numbers 56-60, 62-79, 82, or 83.

6. Use of an agent according to claim 1, wherein the intravenous contrast medium has a molecular weight of 10,000 to 80,000 D.

7. Use of an agent according to claim 1, wherein the intravenous contrast medium is present in more highly-molecular structures.

8. Use of an agent according to claim 7, wherein the intravenous contrast medium is present in the form of molecule associates, liposomes, nano- or microparticles.

9. Use of intravenous contrast media according to claim 1, wherein they are present in an x-ray opacity that corresponds to 100 mg of iodine/ml to 500 mg of iodine/ml.

10. Use of intravenous contrast media according to claim 2, wherein they are present at a concentration of 100 mg of iodine/ml to 500 mg of iodine/ml.

11. Use of intravenous contrast media according to claim 2, wherein they are administered at a dose that corresponds to 150 mg of iodine/kg to 1500 mg of iodine/kg of body weight.

12. Use of intravenous contrast media according to claim 3, wherein they are present at a concentration of 100 mg of bromine/ml to 500 mg of bromine/ml.

13. Use of intravenous contrast media according to claim 3, wherein they are administered at a dose that corresponds to 100 mg of bromine/kg to 1500 mg of bromine/kg of body weight.

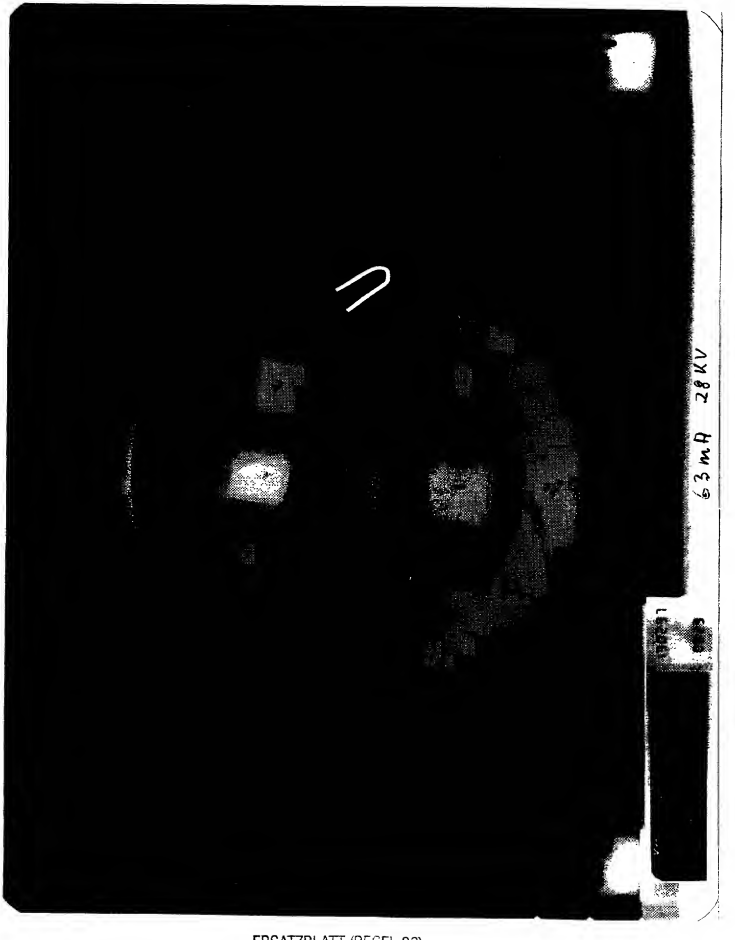
14. Use of intravenous contrast media according to claim 4, wherein they are present at a concentration of 10 mmol - 2 mol/l.

15. Use of intravenous contrast media according to claim 4, wherein they are administered at a dose of 0.1 - 2 mmol/kg of body weight.

16. Use of intravenous contrast media according to claim 5, wherein they are present at a concentration of 10 mmol/l - 2 mol/l.

17. Use of intravenous contrast media according to claim 5, wherein they are administered at a dose of 0.1 - 2 mmol/kg of body weight.

Fig. 1



514128 M1

COMBINED DECLARATION FOR PATENT APPLICATION AND POWER OF ATTORNEY (Includes Reference to PCT International Applications)	ATTORNEY DOCKET NUMBER SCH 1653

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought of the invention entitled

USE OF INTRAVENOUS CONTRAST MEDIA FOR PROJECTION MAMMOGRAPHY

the specification of which (check only one item below):

☐ is attached hereto.

☒ was filed as United States application

Serial No 09/446,328

on 20 DECEMBER 1999

and was amended

on _____ (if applicable)

☒ was filed as PCT international application

Number PCT/EP98/03658

on 19 June 1998

and was amended under PCT Article 19

on _____ (if applicable)

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, §1.56(a).

I hereby claim priority benefits under Title 35, United States Code §119 of the following United States Provisional Application and of any foreign application(s) for patent or inventor's certificate or of any PCT international application(s) designating at least one country other than the United States of America listed below and have also identified below any foreign application(s) for patent or inventor's certificate or any PCT international application(s) designating at least one country other than the United States of America filed by me on the same subject matter having a filing date before that of the application(s) of which priority is claimed

PRIOR U.S. PROVISIONAL AND FOREIGN/PCT APPLICATION(S) AND ANY PRIORITY CLAIMS UNDER 35 U.S.C. 119:

COUNTRY (if PCT indicate PCT)	APPLICATION NUMBER	DATE OF FILING (day, month, year)	PRIORITY CLAIMED UNDER 35 U.S.C. 119
Europe	97250190.2	20 June 1997	☒ YES ☐ NO
			☐ YES ☐ NO
			☐ YES ☐ NO
			☐ YES ☐ NO
			☐ YES ☐ NO

Combined Declaration For Patent Application and Power of Attorney (Continued)
(Includes Reference to PCT International Applications)

ATTORNEY'S DOCKET NUMBER: SCH 1653

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) or PCT international application(s) designating the United States of America that is/are listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in that/those prior application(s) in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations §1.56(a) which occurred between the filing date of the prior application(s) and the national or PCT international filing date of this application

U.S. APPLICATION NUMBER	U.S. FILING DATE	PATENTED	PENDING	ABANDONED

PCT APPLICATION NO.	PCT FILING DATE	U.S. SERIAL NUMBERS ASSIGNED (if any)			

POWER OF ATTORNEY: As a named inventor, I hereby appoint J. William Millen (19,544), John L. White (17,746), Anthony J. Zelano (27,969), Alan E. Branigan (20,565), John R. Moses (24,983), Harry B. Shubin (32,004), Brion P. Heaney (32,542), Richard J. Traverso (30,595), John A. Sopp (33,103), Richard M. Lebovitz (37,067), John H. Thomas (33,460), Catherine M. Joyce (40,668), James T. Moore (35,619), and Nancy Axelrod (44,014) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith.

Send Correspondence to: MILLEN, WHITE, ZELANO & BRANIGAN, P.C., Arlington Courthouse Plaza I, Suite 1400, 2200 Clarendon Boulevard, Arlington, Virginia 22201

Telephone No.: 703/243-6333

Direct Telephone Calls to: 703/813-5325

2	FULL NAME OF INVENTOR	FAMILY NAME: SPECK	FIRST GIVEN NAME: Ulrich	SECOND GIVEN NAME
0	RESIDENCE & CITIZENSHIP	CITY: Berlin	STATE OR FOREIGN COUNTRY: Germany	COUNTRY OF CITIZENSHIP: Germany
1	POST OFFICE ADDRESS	STREET: Furstendamm 20	CITY: Berlin	STATE & ZIP CODE/COUNTRY: D-13465 Germany
2	FULL NAME OF INVENTOR	FAMILY NAME: VON BRENNDORFF	FIRST GIVEN NAME: Irtel	SECOND GIVEN NAME
0	RESIDENCE & CITIZENSHIP	CITY: Braunschweig	STATE OR FOREIGN COUNTRY: Germany	COUNTRY OF CITIZENSHIP: Germany
2	POST OFFICE ADDRESS	STREET: Hohlbeinstrasse 1	CITY: Braunschweig	STATE & ZIP CODE/COUNTRY: D-38106 Germany
2	FULL NAME OF INVENTOR	FAMILY NAME	FIRST GIVEN NAME	SECOND GIVEN NAME
0	RESIDENCE & CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP
3	POST OFFICE ADDRESS	STREET	CITY	STATE & ZIP CODE/COUNTRY
2	FULL NAME OF INVENTOR	FAMILY NAME	FIRST GIVEN NAME	SECOND GIVEN NAME
0	RESIDENCE & CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP
4	POST OFFICE ADDRESS	STREET	CITY	STATE & ZIP CODE/COUNTRY

Combined Declaration for Patent Application and Power of Attorney (Continued)

(Includes Reference to PCT International Applications)

ATTORNEY'S DOCKET NUMBER: SCH 1653

205	FULL NAME OF INVENTOR	FAMILY NAME		FIRST GIVEN NAME	SECOND GIVEN NAME
	RESIDENCE & CITIZENSHIP	CITY		STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP
	POST OFFICE ADDRESS	STREET		CITY	STATE & ZIP CODE/COUNTRY
206	FULL NAME OF INVENTOR	FAMILY NAME		FIRST GIVEN NAME	SECOND GIVEN NAME
	RESIDENCE & CITIZENSHIP	CITY		STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP
	POST OFFICE ADDRESS	STREET		CITY	STATE & ZIP CODE/COUNTRY
207	FULL NAME OF INVENTOR	FAMILY NAME		FIRST GIVEN NAME	SECOND GIVEN NAME
	RESIDENCE & CITIZENSHIP	CITY		STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP
	POST OFFICE ADDRESS	STREET		CITY	STATE & ZIP CODE/COUNTRY
208	FULL NAME OF INVENTOR	FAMILY NAME		FIRST GIVEN NAME	SECOND GIVEN NAME
	RESIDENCE & CITIZENSHIP	CITY		STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP
	POST OFFICE ADDRESS	STREET		CITY	STATE & ZIP CODE/COUNTRY
209	FULL NAME OF INVENTOR	FAMILY NAME		FIRST GIVEN NAME	SECOND GIVEN NAME
	RESIDENCE & CITIZENSHIP	CITY		STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP
	POST OFFICE ADDRESS	STREET		CITY	STATE & ZIP CODE/COUNTRY
210	FULL NAME OF INVENTOR	FAMILY NAME		FIRST GIVEN NAME	SECOND GIVEN NAME
	RESIDENCE & CITIZENSHIP	CITY		STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP
	POST OFFICE ADDRESS	STREET		CITY	STATE & ZIP CODE/COUNTRY

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon

SIGNATURE OF INVENTOR 201	DATE	SIGNATURE OF INVENTOR 207	DATE
X Micah Green	X March 2, 2000		
SIGNATURE OF INVENTOR 202	DATE	SIGNATURE OF INVENTOR 208	DATE
SIGNATURE OF INVENTOR 203	DATE	SIGNATURE OF INVENTOR 209	DATE
SIGNATURE OF INVENTOR 204	DATE	SIGNATURE OF INVENTOR 210	DATE
SIGNATURE OF INVENTOR 205	DATE	SIGNATURE OF INVENTOR 211	DATE
SIGNATURE OF INVENTOR 206	DATE	SIGNATURE OF INVENTOR 212	DATE

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COMBINED DECLARATION FOR PATENT APPLICATION AND POWER OF ATTORNEY
(Includes Reference to PCT International Applications)

ATTORNEY'S DOCKET NUMBER
SCH 1653

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought of the invention entitled:

USE OF INTRAVENOUS CONTRAST MEDIA FOR PROJECTION MAMMOGRAPHY

the specification of which (check only one item below):

☐ is attached hereto.

☒ was filed as United States application

Serial No 09/446,328

on 20 DECEMBER 1999

and was amended

on _____ (if applicable)

☒ was filed as PCT international application

Number PCT/EP98/03658

on 19 June 1998

and was amended under PCT Article 19

on _____ (if applicable)

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, §1.56(a).

I hereby claim priority benefits under Title 35, United States Code §119 of the following United States Provisional Application and of any foreign application(s) for patent or inventor's certificate or of any PCT international application(s) designating at least one country other than the United States of America listed below and have also identified below any foreign application(s) for patent or inventor's certificate or any PCT international application(s) designating at least one country other than the United States of America filed by me on the same subject matter having a filing date before that of the application(s) of which priority is claimed:

PRIOR U.S. PROVISIONAL AND FOREIGN/PCT APPLICATION(S) AND ANY PRIORITY CLAIMS UNDER 35 U.S.C. 119:

COUNTRY (if PCT indicate PCT)	APPLICATION NUMBER	DATE OF FILING (day month year)	PRIORITY CLAIMED UNDER 35 U.S.C. 119
Europe	97250190.2	20 June 1997	☒ YES ☐ NO
			☐ YES ☐ NO
			☐ YES ☐ NO
			☐ YES ☐ NO
			☐ YES ☐ NO

Combined Declaration For Patent Application and Power of Attorney (Continued)

(Includes Reference to PCT International Applications)

ATTORNEY'S DOCKET NUMBER: SCH 1653

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) or PCT international application(s) designating the United States of America that is/are listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in that/those prior application(s) in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations §1.56(a) which occurred between the filing date of the prior application(s) and the national or PCT international filing date of this application

U.S. APPLICATION NUMBER	U.S. FILING DATE	PATENTED	PENDING	ABANDONED

PCT APPLICATION NO.	PCT FILING DATE	U.S. SERIAL NUMBERS ASSIGNED (if any)			

POWER OF ATTORNEY: As a named inventor, I hereby appoint: William Millen (19,544), John L. White (17,746), Anthony J. Zelano (27,969), Alan E. Branigan (20,565), John R. Moses (24,983), Harry B. Shubin (32,004), Brion P. Heaney (32,542), Richard J. Traverso (31,595), John A. Sopp (33,103), Richard M. Lebovitz (37,067), John H. Thomas (33,460), Catherine M. Joyce (40,668), James T. Moore (33,619), and Nancy Axelrod (40,014) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith.

Send Correspondence to: MILLEN, WHITE, ZELANO & BRANIGAN, P.C., Arlington Courthouse Plaza I, Suite 1400, 2200 Clarendon Boulevard, Arlington, Virginia 22201

Telephone No.: 703/243-6333

Direct Telephone Calls to: 703/813-5325

2	FULL NAME OF INVENTOR	FAMILY NAME: SPECK	FIRST GIVEN NAME: Ulrich	SECOND GIVEN NAME	
0	RESIDENCE & CITIZENSHIP	CITY: Berlin	STATE OR FOREIGN COUNTRY: Germany DEX	COUNTRY OF CITIZENSHIP: Germany	
1	POST OFFICE ADDRESS	STREET: Furstendamm 20	CITY: Berlin	STATE & ZIP CODE/COUNTRY: D-13465 Germany	
2	FULL NAME OF INVENTOR	FAMILY NAME: VON BRENNDORFF	FIRST GIVEN NAME: Ingrid	SECOND GIVEN NAME	
0	RESIDENCE & CITIZENSHIP	CITY: Braunschweig	STATE OR FOREIGN COUNTRY: Germany DEX	COUNTRY OF CITIZENSHIP: Germany	
2	POST OFFICE ADDRESS	STREET: Hohlbeinstrasse	CITY	STATE & ZIP CODE/COUNTRY	
2	FULL NAME OF INVENTOR	FAMILY NAME	FIRST GIVEN NAME	SECOND GIVEN NAME	
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0	RESIDENCE & CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP	
4	POST OFFICE ADDRESS	STREET	CITY	STATE & ZIP CODE/COUNTRY	

Combined Declaration for Patent Application and Power of Attorney (Continued)

(Includes Reference to PCT International Applications)

ATTORNEY'S DOCKET NUMBER: SCH 1653

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	RESIDENCE & CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP
	POST OFFICE ADDRESS	STREET	CITY	STATE & ZIP CODE/COUNTRY
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SIGNATURE OF INVENTOR 201	DATE	SIGNATURE OF INVENTOR 207	DATE
SIGNATURE OF INVENTOR 202 Robert Millen	DATE 6. March 2000	SIGNATURE OF INVENTOR 208	DATE
SIGNATURE OF INVENTOR 203	DATE	SIGNATURE OF INVENTOR 209	DATE
SIGNATURE OF INVENTOR 204	DATE	SIGNATURE OF INVENTOR 210	DATE
SIGNATURE OF INVENTOR 205	DATE	SIGNATURE OF INVENTOR 211	DATE
SIGNATURE OF INVENTOR 206	DATE	SIGNATURE OF INVENTOR 212	DATE